PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Swan *et al.*	**Examiner:**	Naff, David M.
Serial No.:	10/723,505	**Group Art Unit:**	1657
Filed:	November 26, 2003		
For:	BIOCOMPATIBLE POLY-MERIZATION ACCELERATORS	**Docket No.:**	SRM0006/US

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I CERTIFY THAT ON June 19, 2009, THIS PAPER IS BEING DEPOSITED WITH THE U.S. POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450

Joni Jurek
JONI JUREK

DECLARATION UNDER 37 C.F.R. § 1.131

Dear Sir:

I, Dale G. Swan, declare the following:

1. I am an applicant of the above-identified patent application.

2. I have worked for SurModics as a research chemist for 21 years; SurModics is the current assignee of the above-identified patent application. I am paid a salary and other compensation for my work for SurModics.

3 I have at least 16 years of experience in developing chemical reagents for use in the body, including reagents for use in polymeric systems for regenerative and drug delivery technologies. I hold a master's degree in organic chemistry, which was awarded from the University of Minnesota in 1970.

4. The invention claimed in the above-identified application was conceived and reduced to practice in the United States of America prior to October, 2002, as indicated by the following facts, supported by attached Exhibits 1-13.

5. All of the work described in Exhibits 1-13 was performed at SurModics, Eden Prairie, Minnesota, U.S.A., prior to October 2002.

6. Exhibits 1-13 include proposals, synthetic schemes, and experimental data describing the preparation of polymerization accelerators having biocompatible functional groups, and the use of these accelerators for preparing biocompatible polymeric matrices, which can be formed in the presence of tissue or cells. The accelerators described in these Exhibits include ones having an N-vinyl amide functionality and a sulfonate functionality.

7. Exhibits 1 and 2 consist of pages 20 and 26, respectively, from my notebook #2683 which were dated and signed prior to October 2002, and which describe a scheme for the synthesis of the biocompatible polymerization accelerator N-vinylsuccinimide-2-sulfonate (NVSS). NVSS has N-vinyl amide and sulfonate functionalities and is specifically described in the above-identified patent application at pages 29-30 (Example 4, compound 4). NVSS falls under the scope of the accelerator recited in claims of the patent application.

8. Exhibits 3-10 consist of pages 21, 26, 27, 30, 31, 37, 39, and 39 (cont.) respectively, from my technical assistant's notebook #2706 which were dated and signed prior to October 2002, and which describe the details of the laboratory synthesis of NVSS.

9. Exhibit 11 consists of page 30 from my notebook #2683 which were dated and signed prior to October 2002, and which describe a scheme for the synthesis of the biocompatible polymerization accelerator potassium 3-({3-[formyl(vinyl)amino] propanoyl}oxy)propane-1-sulfonate (NVF-SPA), as well as the details of its laboratory synthesis. NVF-SPA has N-vinyl amide and sulfonate functionalities and is specifically described in the above-identified patent application at page 30 (Example 5, compound 5). NVF-SPA falls under the scope of the accelerator recited in claims of the patent application.

10. Exhibit 12 consists of a SurModics Intellectual Property and Proprietary Product Idea Form (the SurModics IP Form) that was dated and signed prior to October 2002. The SurModics IP Form describes the synthesis of biocompatible polymerization accelerators, including ones having N-vinyl amide and sulfonate functionalities. The SurModics IP Form also describes the use of biocompatible polymerization accelerators for preparing protective hydrogel coatings around cells.

11. Exhibit 13 consists of page 79 from my technical assistant's notebook which was dated and signed prior to October 2002, which describes compositions that include the polymerizable material hyaluronic acid macromer and the polymerization accelerator NVSS. This composition falls under the scope of the composition recited in claims of the patent application, and is described in the above-identified patent application at page 32 (Example 9). The composition was polymerized to form a biocompatible polymeric matrix, which can also be formed in the presence of tissue or cells.

12. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements have been made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or patent issuing thereon.

June 2, 2009
Date

Dale G. Swan
Dale G. Swan

On this 2nd day of June, 2009, before me personally appeared Dale G. Swan, to me known to be the person described in and who executed the foregoing instrument and acknowledged that he executed the same as her free act and deed.

Patricia M. Best
Notary Public

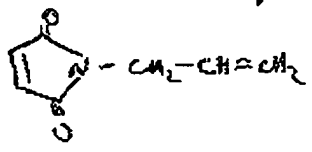
PATRICIA M. BEST
Notary Public
Minnesota
My Commission Expires January 31, 2010

#49537v5

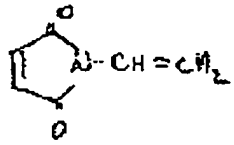
TITLE Idea Crosslinking accelerators Project No. _____ Book No. 2683 20

From Page No. .... see page 16

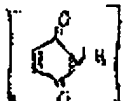
a simple N-Vinyl crosslinker shown below may act as accelerators for matrix applications are shown below.



N-allyl maleimide



N-Vinyl maleimide

a sample of maleimide  was given to M. Benkati and to test as an accelerator for matrix forming.

To Page No. .....

Witnessed & Understood by me, Date Invented by Date

Recorded by

Exhibit 1

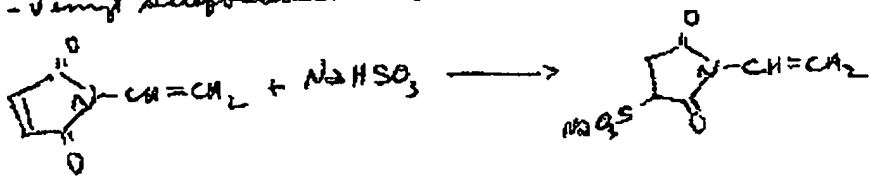
Project No. ....
Book No. ....

26

TITLE Idea

From Page No. ...

Ron Ofstead suggested converting N-Vinyl-maleimide to N-Vinyl sulfosuccinimide



To Page No. ....

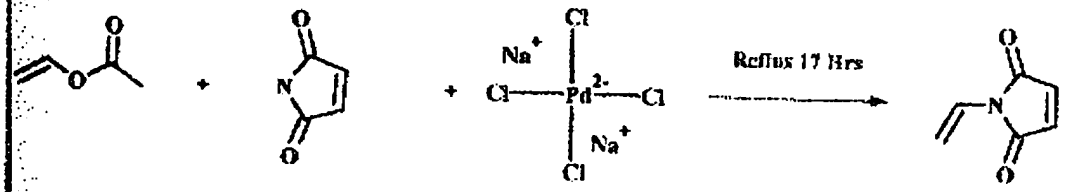
Witnessed & Understood by me.	Date	Invented by	Date
Jerome E Bell		Recorded by Dale Ivan	

Exhibit 2

TITLE Vinyl-Maleimide Project No. TPM0100 Book No. 2706 21

From Page No. 2705

Vinyl-Maleimide.SK2



86.089 g/mole	97.072 g/mole	294.210 g/mole	123.109 g/mole
35.5 g (~38 ml)	10 g	0.25 g	12.7 g (theory)
412.0 mmole	103.0 mmole	0.85 mmole	103.0 mmole (theory)

In a 100 ml RB flask with magnetic stir bar & reflux condenser were placed 10.0075 g Maleimide (Lot # 90009887), 0.24960 g Na_2PdCl_4 & 35.5 g. vinylacetate (Lot # 10224 DG). Stir & heat to refluxing. Refluxing started at 8.50 a.m. Boil. point of vinyl acetate = 72-73°C

Off 1.30 p.m. – Rx turn to dark red with some solid(s) Continue refluxing to total 17 hours.

Refluxing stop at 1.50 p.m – should be shut off 7 a.m. – Rx was still refluxing.

Remove heating & let cool. Filter off Rx, remove excess of vinylacetate on a Rotovap at T=40°C under air bleeding into the flask. We got ~15 g. residue in the flask. Add 45 ml Et_2O, stir in IPA-dry ice bath at T=-20°C for 30 min. Filter off solid, dry at RT under water aspirator to gave 5.0 g. yellow crystals /2706-21/

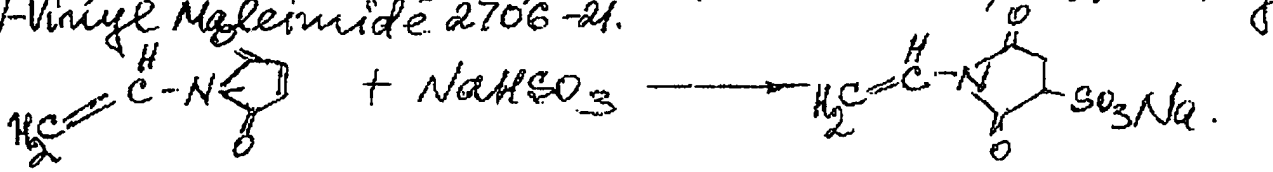
To Page No. 22

Witnessed & Understood by me,	Date	Invented by	Date
Dal Ivan		Recorded by D. Stehman	

Exhibit 3

From Page No. —

Rx#1 similar as Rx#3 in NMR tube, but using N-Vinyl Maleimide 2706-21.



F.W. = 123.11	104.06	225.15
50 mg	50.8 mg	91.41 mg
0.406 mmole	0.488 mmole	0.406 mmole

We couldn't prepare solution 50 mg N-Vinyl Maleimide in 1.0 mL D_2O — ND!

In a NMR tube was placed 50 mg N-Vinyl Maleimide & add solution of 51.6 mg $NaHSO_3$ in 1.0 mL D_2O. Vortex & heat at 50°C water bath for 10 min, almost all was dissolved, filter off through pipet filter to another NMR tube & submit for NMR.
Results see p. 25 back side.

Rx at RT very slow.

Rx#2 1 g N-Vinyl Maleimide (0.00812M) 2706-21 + solution 1.2 g $NaHSO_3$ in 20 mL di-H_2O (0.0098M)
Shake at 55°C from 4 p.m. over weekend.

Rx had very small amount of solid; Rx was filtered off & water was removed with 2 × 20 mL $CHCl_3$ (at 60°C under water aspirator).
Got 1.71 g. yellowish residue (2706-26-1) or 93.4% from theory - theory yield 1.829 g.
Prepare 30 mg/0.7 mL D_2O for NMR (see p. 26 back side)

To Page No. 27

Witnessed & Understood by me, Deb Swan — Date — Invented by — Date — Recorded by C. Stelmack

Exhibit 4

From Page No. 26

Product 2706-26-1, has some impurities, need be purified.

1.71 g 2706-26-1 was dissolved in 5.1 mL H_2O, then was added 8 mL CH_3OH, heat at 60°C water bath. All was dissolved, cool solution in ice-water bath. Filter off solid, dry at 60°C, to give 430 mg of offwhite crystals /2706-26-2/.

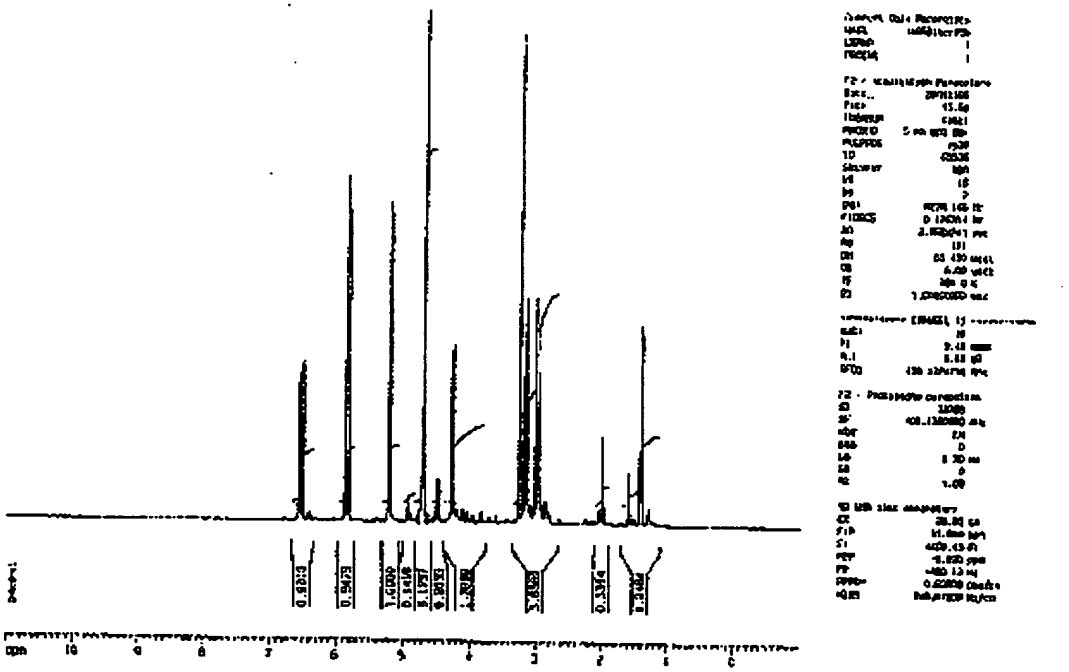
From filtrate we got 520 mg offwhite crystals /2706-26-3/.

Prepare NMR samples.

2706-26-3 cleaner than 2706-26-1; 2706-26-2 impurity.

2706-26-3 was given to MJB for testing.

DS



Witnessed & Understood by me, Date

Invented by Date

Recorded by

Exhibit 5

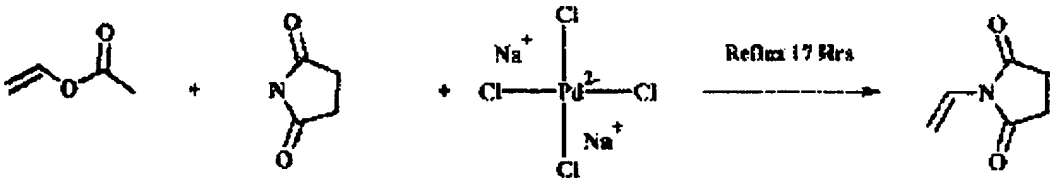
TLE Vinyl-Succinimide Project No. TTPM0100 Book No. 2706 30

From Page No. Ref 2706-24

GSE

DI

Vinyl-succinimide.SK2



26.30 mg

999.97 eq

86.089 g/mole	99.088 g/mole	294.210 g/mole	125.125 g/mole
3.55 g (~3.8 ml)	1.0 g	0.025 g	1.25 g (theory)
41.29 mmole	10.8 mmole	0.0085 mmole	10.0 mmole (theory)

In a 25 mL RB flask with magnetic stir bar were placed all ingredient. Stir & heat to refluxing. Refluxing from 3.30 p.m.

7.10 a.m. - cool Rx. Filter off through pipet filter & wash with 2×5 mL CH_2Cl_2. Remove solvent on a Rotovap at 40°C under water aspirator with air bleeding in a flask. Get 1.3 g. yellow liquid.

Add 4.5 mL Et_2O & stir in dry ice bath. Filter off solid, dry to gave 1.04 g. brownish solid / 2706-30/.

Prepare 30 mg/0.75 mL D_2O for NMR /see p.29 back side/.

Product looks good by NMR.

TLC was developed in $CH_3OH/CHCl_3$ = 1/99 /see p.28B/ & $CH_3OH/CHCl_3$ = 10/90.

We have one spot.

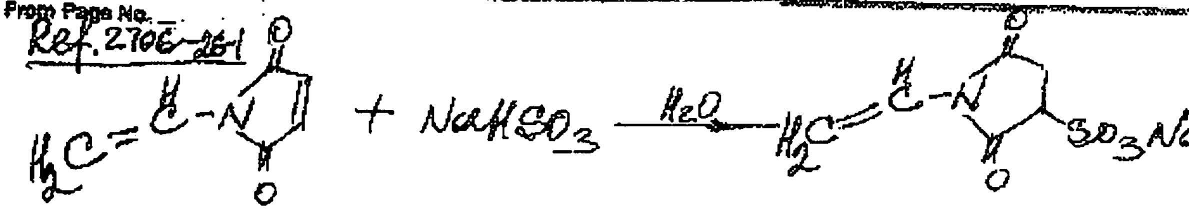
To Page No. 33

Witnessed & Understood by me,	Date	Invented by	Date
Dal Swan		Recorded by S. Gilman	

Exhibit 6

TITLE Sulfo-N-Vinyl ~~Maleimide~~ Succinimide Project No. IIPM0100 Book No. 2706

From Page No. ___
Ref. 2706-26



123.11	104.06	225.15
1.0 g	1.02 g	1.828 g (theory)
0.00812 M	0.0098 M	0.00812 M (—"—)

To 1.0 g N-Vinyl Maleimide (#2706-21) was added solution 1.2 g $NaHSO_3$ in 20 mL DI-H_2O, vortex after 5 min then placed at 55°C oven on a Orbit Shaker & shaked from 2.15 p.m.

Prepare TLC, comparing Rx & starting material.

Filter off Rx-solution was slightly cloudy. Remove water with 2×20 mL $CHCl_3$, dry on a Rotovap at 60°C to gave 1.67 g light yellow crystals (2706-31).

Prepare 30 mg/0.75 mL D_2O for NMR (see p. 30 back side).

Product is good.

500 mg was given to MJB for testing.

30 mg of 2706-31 was dissolved in 300 µL DI-H_2O. Added 6.0 mL of brine solution — no precipitation.

1 mL Methanol + 5 mL of brine sol. → NaCl precipitated.

③. 30 mg of 2706-31 was dissolved in 300 µL DI-H_2O. Added 20 mL sat. K_2CO_3 — no precipitation.

To Page No. ___

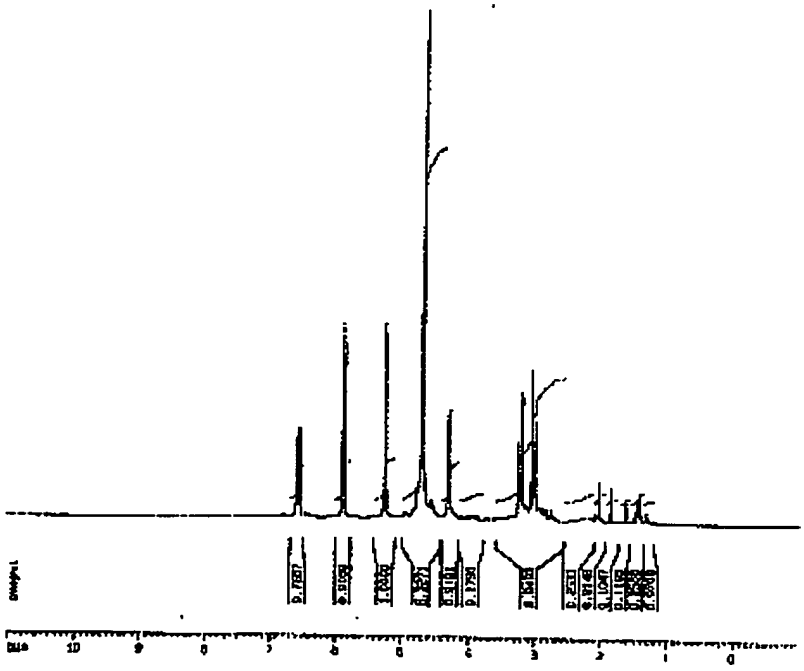
Witnessed & Understood by me, Dab Saran | Date | Invented by | Recorded by S. Stelman | Date

Exhibit 7

To 1.75 g Vinyl-Maleimide (2706-21) was added ~~solution~~ 35 mL bi-H_2O + 2.1 g $NaHSO_3$, vortex for 5 min, then shake ON at 55°C oven from 3.30 p.m.

Filter off ~~foam~~ insoluble. Remove water with 2×35 mL $CHCl_3$, dry on a Rotavap at 60°C to gave 3.0 g. light yellow crystals (2706-37) (theory yield 3.2 g).

Product looks good - Was given to MB for testing.



To Page No.

Witnessed & Understood by me. Date Invented by S. Ekelman Notes

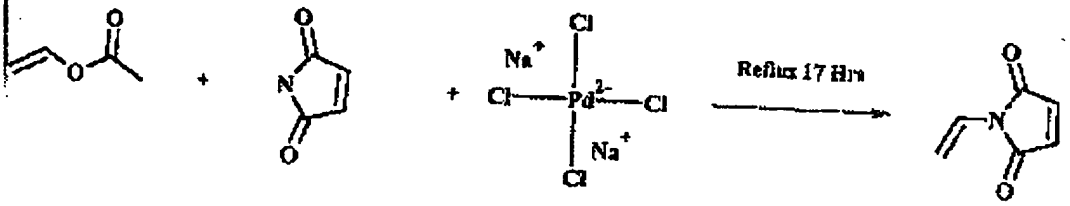
Dale Swan Recorded by S. Ekelman

TITLE N-Vinyl Maleimide Project No. TPM0100
Book No. 2706 39

From Page No. Ref. 2706-21

SSG DS SSG

Vinyl-Maleimide.SK2



Acet. wt Maleimide 10.0000 g
Na_2PdCl_4 249.69 g

86.089 g/mole	97.072 g/mole	294.210 g/mole	123.109 g/mole
35.5 g (~38 ml)	10 g	0.25 g	12.7 g (theory)
412.0 mmole	103.0 mmole	0.85 mmole	103.0 mmole (theory)

In a 100 ml RB flask with magnetic stir bar & reflux condenser were placed 10.0000 g Maleimide (Lot # 00009887), 0.24969 g Na_2PdCl_4 & 35.5 g. vinylacetate (Lot # 10224 DG). Stir & heat to refluxing. Refluxing started at 18.50 p.m. Boil. point of vinyl acetate = 72-73°C. T of oil bath = 85°C.

7.15 a.m. (~17.5 hours of refluxing) - remove oil bath, let cool, filter off brown solid, remove excess of vinylacetate at 40°C with air bleeding in a flask. We got ~ 14.5 g. residue in the flask. Add 45 ml Et_2O, stir in IPA-dry ice bath at T = -20°C for 30 min.

Filter off solid, dry at RT under water aspirator to gave 5.50 g. yellow crystals /2706-39/. Filtrate was stirred for 30 min more in IPA-dry ice bath at T = -20°C. Filter off, dry to gave 1.4 g. yellow crystals /39-1/. Ether was removed to gave 3.0 g. yellow /2706-39-2/

To Page No. 2-0

Witnessed & Understood by me.	Date	Invented by	Date	Back Side.
Dat Iwa		Recorded by S. Stelman		

Exhibit 9

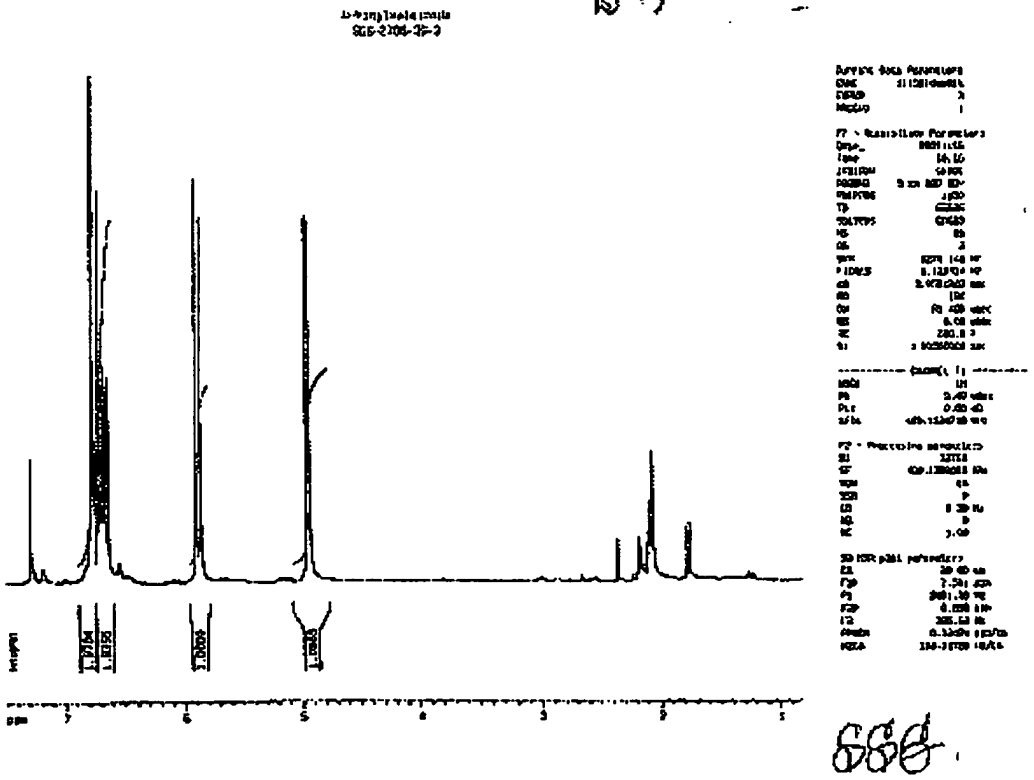
From p. 39.

solids (2706-39-B). Seems that product started to polymerize.

Redissolve solid (39-3) in 25 mL $CHCl_3$ by shaking on an Orbit Shaker for 20 min, filter off solids that didn't dissolve.

Remove $CHCl_3$ on a Rotovap at RT under water aspirator with air bleeding into a flask. Traces of solvent were removed by sweeping ON with air to gave 1.41 g. yellow solid (2706-39-3A).

D1

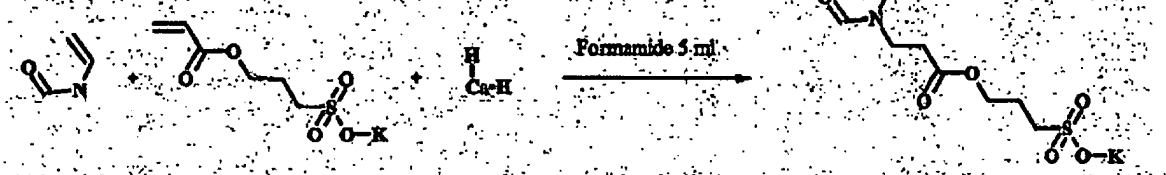


686

From Page No. _ see pages 16-19

Purpose: to determine if ✱ formamide would be a solvent for the reaction of N-Vinylformamide and the potassium salt of sulfopropyl acrylate.

NVF-rx2.sk2



1.014 g/ml			
N-vinylformamide (NVF)	Sulfopropylacrylate	Calcium hydride	
71.08 g/mole	232.30 g/mole	42.09 g/mole	313.38 g/mole
1.42 g (1.40 ml)	4.646 g	0.030 g	6.07 g (theory)
20.0 mmole	20.0 mmole	0.713 mmole	20.0 mmole (theory)

Procedure: The ingredients were stirred at an unknown temperature (25 to 90 C most likely). After 20 hours 0.1 ml was treated with 0.5 ml methanol and 0.5 ml chloroform. Removal of the volatiles gave 99 mg residue 2683-30-1 (mainly formamide any product?). The residue was washed with a second portion of methanol 0.5 ml and chloroform 0.5 ml. The clear liquid was again removed and evaporated to give 2683-30-2 (12.9 mg). The residue after two washings was dried to give 2683-30-3 (6.4 mg) Three samples were made for NMR comparisons- potassium sulfoacrylate 2683-30-4, formamide 2683-30-5, and N-vinyl formamide 2683-30-6. A final reaction sample 0.1 ml worked up with methanol and chloroform was labeled 2683-30-7. Sample 1,2 and 7 appeared to show a new four lined NMR peak at ~6.95 ppm. This new NMR peak may be evidence for the presence of the desired product.,

JCB

To Page No. _____

Witnessed & Understood by me,	Date	Invented by	Date
Veronica Bek		Recorded by Deb Swan	

Exhibit 11

SurModics Intellectual Property and Proprietary Product Idea Form (2)

Originator(s) **Date**

Ron Ofstead and Dale Swan

Title/Key Words

N-vinylamides as accelerators in matrix formation

Reference (Personal Notes/Notebook Number and Pages)

2683-16,20,26

Brief Description

Cells can be covered with a protective hydrogel coating. The polymerization of PEG-triacrylate around the cells is accelerated by the addition of N-vinylamides. In addition the presence of sulfonate containing monomers (ie AMPS) have been useful in improving biocompatibility. The idea was to synthesize reagents containing N-vinylamides and sulfonate functionality. The attachment of figures 1 to 4 show the reactions used to make N-vinyl amides.

Advantages and Features

The materials proposed can be made in one or two steps from available materials. Preliminary tests indicated firm gels resulted from the cyclic products synthesized.

Reduced to Practice (Date/Notebook Number and Pages)

2706-21, 26, 30, 31, 37, 39 from

Submitted by

Signature	Printed Name	Originator(s)	Date
Dale Swan	DALE SWAN		
R. Ofstead	R. Ofstead		

Read and Understood by

Signature	Printed Name	Witness	Date
Anthony Dallmier	Anthony Dallmier		
Jerome C. Behrens	Jerome C. BEHRENS		

PROPRIETARY
SurModics, Inc.

Exhibit 12

m Page No. 78

Based on the two previous batches made [#1 looked great; #2 doesn't work in this system]

~~Ermmee~~ cont. designed a set of experiments to test the synthesis of the accelerant. Started up 5 solutions @ different levels of sulfo-n-vinyl-succinimide. Lot # 2703-16-(1,2,3,4,&5)

recovered ~500mg of each. Added ~9mg of each to 32% HA, 0.25% MPA solution, & let mix for 1 hour on 37°C shaker (Amber vials labeled 1-5, to represent the vial - see previous page for vial set-up)

After mixing, adding 75µl to white teflon mold, & illuminate for 45sec

1) Soft, no matrix, bleaching
2) Soft, matrix, no bleaching
3) great, firm matrix,
4) " "
(5) " "

- solutions set o/N @ Room Temperature. all solutions, when illuminated, looked similar as first test

solutions mixed o/N @ 37°C shaker - when illuminated, solutions looked similar; #3 may have been a bit softer, but hard to tell.

Witnessed & Understood by me, Date Invented by Date

Exhibit 13